REMARKS

I. Status Summary

Claims 1-4 and 6-10 are pending in the subject U.S. patent application and have been examined by the United States Patent and Trademark Office (hereinafter "the Patent Office") in a Final Official Action dated April 10, 2008 (hereinafter the "Final Official Action").

Claim 6 has been objected to upon the contention that it is directed to unelected subject matter.

Claims 1-4 and 7-10 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the specification does not enable the full scope of the claims.

Claims 1-4 and 7-10 have been rejected under 35 U.S.C. § 112, second paragraph, upon the contention that certain phrases recited in the claims are unclear.

Claim 6 has been canceled without prejudice.

Claims 1 and 7 have been amended. Support for the amendments can be found throughout the specification as filed, including particularly at page 11, line 27, through page 12, line 4. Additional support can be found on page 25, lines 8-11; page 29, lines 5-7, and page 30, line 21, through page 31, line 1. As such, no new matter has been added by the amendments to the claims.

Reconsideration of the application as amended and in view of the remarks presented hereinbelow is respectfully requested.

II. Response to the Objection to Claim 6

Claim 6 has been objected to upon the contention that it is directed to unelected subject matter. Applicants have canceled claim 6 without prejudice. Thus, it is believed that the instant objection to claim 6 has been addressed, and as such, applicants respectfully request that it be withdrawn at this time.

III. Response to the Enablement Rejection

Claims 1-4 and 7-10 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the specification does not enable the full scope of the claims. The Patent Office makes the following assertions in support of the instant rejection:

- the only purpose for the method claimed is to repopulate the treated embryo with donor PGCs from a different strain or species of avian to make a chimeric avian;
- the specification does not provide a use for the method claimed without making a chimeric avian;
- the specification does not teach an enabled use for these embryos without repopulating the embryo with donor PGCs;
- the art is silent regarding treating an avian embryo to decrease PGC numbers/development and repopulating the treated embryo with donor PGCs from a different strain or species of avian to make a chimeric avian;
- applicants fail to teach how to determine whether PGC numbers had decreased *in ovo* without sacrificing the embryo;
- applicants fail to teach how to determine whether amounts of antigens or antibodies that decrease endogenous PGC numbers had been injected or obtained as claimed without sacrificing the embryo;
- survival of the embryo is essential to making a chimeric avian - the sole disclosed use for the method claimed;
- the specification fails to overcome the absence in the art by reasonably teaching injecting donor PGCs into a treated embryo will repopulate the treated embryo to produce a viable chimeric avian;
- merely injecting donor PGCs and assessing PGC repopulation as suggested is inadequate to indicate PGCs would successfully repopulate the embryo in which PGCs had been destroyed or that a viable avian would be obtained;
- it is not readily apparent from the specification that donor PGCs will target the proper position in the embryo to successfully replace the PGCs destroyed by the treatment so that a viable chimeric avian will be obtained;

- if the method described does not produce viable chimeras, it would require those of skill undue experimentation to determine how to fix the problem because the specification provides no additional suggestions; and
- accordingly, the claims are not enabled for its sole intended use; decreasing PGC numbers in an avian embryo for the purpose of repopulating the embryo with donor PGCs and obtaining a viable chimeric avian.

After careful consideration of the rejection and the Patent Office's basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

First, applicants respectfully traverse the Patent Office's assertion that the only purpose for the method claimed is to repopulate the treated embryo with donor PGCs from a different strain or species of avian to make a chimeric avian. Applicants respectfully submit that there is no basis for the Patent Office to conclude that a different strain or species of avian must be used as a PGC donor vis-à-vis the recipient avian. The Patent Office has pointed to no language in the instant specification to support this contention.

On the contrary, applicants respectfully submit that the specification as filed clearly discloses that the donors and recipients can be from the same species or from different species. As set forth on page 4, lines 24-27 of the instant specification, "[i]n one embodiment, the donor PGCs are from the same avian species as the recipient embryo. In another embodiment, the donor PGCs are from a different avian species as the recipient embryo". Additionally, applicants respectfully submit that Example 3 explicitly discloses using chickens as both the PGC donors and the recipients.

Similarly, applicants respectfully submit that the Patent Office's assertion on page 6 of the Final Official Action that page 34, lines 19-26 of the instant specification "is limited to using donor PGCs from a different strain or species. Nowhere is it explicitly or implicitly taught that the donor PGCs are the same species as the avian embryo" is also believed to be without merit. Applicants respectfully submit that the relevant passage recites the following:

> In particular embodiments of the presently disclosed subject matter, the number of endogenous PGCs in the recipient bird is reduced prior to introduction of the donor PGCs. In this manner, the donor PGCs can repopulate the gonads of the recipient bird and can increase the efficiency of producing chimeric birds and the proportion of gametes (and offspring) that are derived from the donor bird.

Applicants respectfully submit that there is no basis for concluding that this passage is limited to producing interstrain or interspecific chimeras, nor is there any disclosure in the adjoining sections of the specification that would compel this conclusion. Applicants respectfully submit that if the Patent Office is interpreting either of the terms "donor" or "recipient" as requiring one to be of a different strain or species as the other, there is no support for this interpretation in the instant specification.

Accordingly, applicants respectfully submit that the Patent Office's assertion that the instant specification only discloses interstrain or interspecific chimeras is believed to be inaccurate, and thus does not support the instant rejection.

Turning to the next series of assertions, the Patent Office contends that: the specification does not provide a use for the method claimed without making a chimeric avian; the specification does not teach an enabled use for these embryos without repopulating the embryo with donor PGCs; the art is silent regarding treating an avian embryo to decrease PGC numbers/development and repopulating the treated embryo with donor PGCs from a different strain or species of avian to make a chimeric avian; applicants fail to teach how to determine whether PGC numbers had decreased *in ovo* without sacrificing the embryo; applicants fail to teach how to determine whether amounts of antigens or antibodies that decrease endogenous PGC numbers had been injected or obtained as claimed without sacrificing the embryo; and, survival of the embryo is essential to making a chimeric avian - the sole disclosed use for the method claimed. Applicants respectfully submit that contrary to the Patent Office's assertions, one of ordinary skill in the art would have known how to decrease endogenous PGC numbers by immunizing female avians with antigens that are associated with PGCs and repopulate recipient avians with donor PGCs, and further would have been able to accomplish both of these goals to produce chimeric avians with only routine experimentation after consideration of the instant specification.

In support of this contention, applicants hereby submit a DECLARATION OF JAMES N. PETITTE, PH.D. PURSUANT TO 37 C.F.R. §1.132 (hereinafter the "Petitte Declaration"). Turning first to the issue of decreasing PGC numbers in embryonic avians, applicants respectfully submit that Point 6 of the Petitte Declaration provides evidence that as of the priority date of the instant application, (*i.e.*, as of January 2003), one of ordinary skill in the art was aware of certain techniques for treating embryonic avians to decrease PGC numbers and/or development. Exemplary methods described in the Petitte Declaration and the references cited therein include surgical removal of the germinal crescent, treatment with ultraviolet or laser light, and exposure to busulfan (Bu).

Next, applicants respectfully submit that as of the priority date of the instant application, one of ordinary skill in the art would have known that PGCs could be transferred to recipient avians, where they would migrate to the genital ridge and take place in normal gonadal development. For example, Vick *et al.* (1993) *Journal of Reproduction and Fertility* 98:637-641, a true and accurate copy of which is submitted herewith as **Exhibit C** of the Petitte Declaration, and Naito *et al.* (1994) *Molecular Reproduction and Development* 39:153-161, a true and accurate copy of which is submitted herewith as **Exhibit F** of the Petitte Declaration, both describe transfers of PGCs from White Leghorn chickens to and/or from Rhode Island Red or Barred Plymouth Rock chickens. Each publication reports the production of germline chimeric chickens, indicative of the fact that the transferred PGCs, which were transferred into the bloodstream of the recipient embryos, properly migrated to and repopulated the embryonic gonad.

Applicants respectfully submit that as set forth the Petitte Declaration, one of ordinary skill in the art would also have known how to repopulate a treated embryo with donor PGCs from a different strain or species of avian to make a chimeric avian. Point 7 of the Petitte Declaration discusses **Exhibit C** and **Exhibit F**, and points out that both of these publications describe inter-strain transfers of PGCs in chickens. Point 8 of the Petitte Declaration also provides evidence that interspecific chimeras can be produced using PGC transfer. As set forth therein, **Exhibit G** of the Petitte Declaration, which is a true and accurate copy of Section 3.5 of a doctoral thesis of Susan Cardoso D'Costa

submitted to the North Carolina State University in 1999, describes techniques that can be employed for producing interspecific chimeras between turkeys and chickens. U.S. Patent No. 6,354,242, a true and accurate copy of U.S. Patent No. 6,354,242 is being submitted herewith as **Exhibit H**, also describes such techniques.

In view of these references, applicants respectfully submit that the Patent Office's contention that after review of the instant specification, one of ordinary skill in the art would have required undue experimentation to perform the methods of claims 1 and 7 is believed to be without merit.

Continuing, the Patent Office asserts that applicants fail to teach how to determine whether PGC numbers had decreased *in ovo* without sacrificing the embryo. Applicants respectfully disagree. Initially, it is noted that there is no requirement that the determination of a decrease in PGC number itself be performed *in ovo*. Rather, applicants respectfully submit that the techniques disclosed for visualizing PGC numbers *in ovo* can be employed on a subset of treated animals, and the results of the tests performed on these avians can be extrapolated with a high degree of predictability to similar treated avians that are permitted to hatch.

Additionally, the degree of germline chimerism (*i.e.*, the contribution of the donor PGCs to the recipient gonad) is easily assayable by breeding the chimeras once they attain sexual maturity. Applicants respectfully submit that standard molecular biology techniques can be employed for assaying germline chimerism.

Therefore, applicants respectfully submit that that Patent Office's assertions with respect to determining whether PGC numbers had decreased *in ovo* without sacrificing the embryo are also believed to be without merit.

Next, the Patent Office asserts that applicants fail to teach how to determine whether amounts of antigens or antibodies that decrease endogenous PGC numbers had been injected or obtained as claimed without sacrificing the embryo; how to use the assay on page 54 to determine the amounts of antigen or antibodies required to decrease endogenous PGC numbers without sacrificing the embryo; that it is not readily apparent how to determine the values of antigens or antibodies required to decrease PGC numbers as claimed using the assay on page 54 such that a chimeric avian could be made; and that without such guidance, the specification has left those of skill with

undue experimentation to determine how to decrease PGC numbers in an avian embryo as claimed without sacrificing the embryo.

Applicants respectfully disagree. Particularly, applicants respectfully submit that the specification as filed teaches how to immunize female avians. The specification as filed in combination with the skill of the ordinary artisan also provides techniques for depleting PGCs in recipient avians, for repopulating the recipient avian with donor PGCs, and for assessing the relative contribution of the donor PGCs to the germline of the embryos (*e.g.*, by histology or by breeding). As such, applicants respectfully submit that after consideration of the instant specification, one of ordinary skill in the art would know how to determine whether the donor PGCs had repopulated the recipient avian, and if desired, could also determine whether the efficiency of repopulation had been enhanced by the immunization of the female avian. A simple breeding experiment using non-treated controls could be used to assess the efficiency of repopulation by the donor PGCs by assessing the transmission of the donor genome by the chimeras. If the treatment was successful, the treated chimeras would transmit the donor genome to the next generation at a higher frequency than would the untreated control chimeras. This enhancement would be attributed with a high degree of confidence to a decrease in PGC numbers and/or development that resulted from the immunization of the female avians.

Therefore, here as well, applicants respectfully submit that the Patent Office's contentions in support of the instant rejection are believed to be without merit.

Summarily, applicants respectfully submit that the assertions that the Patent Office has presented in support of the instant rejection fail to support the contention that one of ordinary skill in the art would have required undue experimentation to practice the methods of claims 1 and 7. Accordingly, applicants respectfully submit that the Patent Office has not presented a *prima facie* case of lack of enablement of claims 1-4 and 7-10. Thus, applicants respectfully request that the instant rejection of claims 1-4 and 7-10 be withdrawn, and further that the claims be allowed at this time.

IV. Response to the Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1-4 and 7-10 have been rejected under 35 U.S.C. § 112, second paragraph, upon the contention that certain phrases appearing in the claims render the claims indefinite. Particularly, the Patent Office has asserted that the phrases "sufficiently high concentration of antibodies specific for the antigen to modulate the numbers [or development] of endogenous PGCs in an avian embryo" and "specific for the antigen to decrease endogenous PGC numbers" in claims 1 and 7 are unclear.

After careful consideration of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and submit the following remarks.

IV.A. Response to the First Rejection

According to the Patent Office, the metes and bounds of what applicants consider "sufficiently high concentration of antibodies specific for the antigen to decrease the PGC numbers [or development] in an avian embryo" (claims 1 and 7) remain unclear. The Patent Office contends that the concentration of antibodies required to decrease the number or development of PGCs is not set forth in the specification or the art at the time of filing. The Patent Office further contends that those of skill would not be able to determine when the concentration of antibodies obtained was infringing on the claim.

Applicants respectfully disagree. Applicants respectfully submit that the methods of claims 1 and 7 relate to producing in a female avian an immune response against an antigen associated with primordial germ cells (PGCs) by immunizing the female avian with the antigen. While applicants do not wish to be limited to any particular theory of operation, it is believed that immunization of the female avian with the antigen results in deposition of anti-antigen antibodies in the eggs produced by the female. These anti-antigen antibodies bind to the antigens associated with PGCs in the embryonic avian as it develops within the egg. The binding of the antibodies to the antigens in the embryo results in a decrease in PGC numbers in the developing avian as per claim 1 and/or an inhibition in PGC development as per claim 7.

A consequence of this treatment is therefore that the embryonic gonad becomes hypo-colonized with endogenous PGCs as a result of a lower than normal number of

PGCs migrating to the genital ridge and/or correctly developing once they reach the genital ridge. This hypo-colonization enhances the likelihood that when transferred to a recipient embryo, the donor PGCs will colonize the gonads of the recipient to at least a greater degree than they would have had the recipient's endogenous PGCs not been affected.

Stated another way, applicants respectfully submit that when the instantly claimed methods are practiced, the percentage of donor PGCs present in the recipient gonad (and hence the percentage of donor-derived germ cells) is greater relative to endogenous PGCs than if the recipient's own PGCs were not affected by the immunization of the female avian that produced the egg in which the recipient develops. As a result, the percentage of donor-derived offspring that is produced is also correspondingly enhanced.

Therefore, applicants respectfully submit that contrary to the Patent Office's apparent belief, one of ordinary skill in the art could easily determine if they are infringing the instant claims by breeding the recipient embryos once they reach sexual maturity. Thus, also contrary to the Patent Office's assertion, there is no requirement that an absolute concentration of antibodies be disclosed in the specification.

Furthermore, applicants respectfully submit that the Patent Office's assertion that the specification does not teach how to determine whether PGCs numbers decrease without sacrificing the avian dos not support the instant rejection. Applicants respectfully submit that the induction of an immune response by administering antigenic compounds is sufficiently predictable that one of ordinary skill in the art would have a reasonable expectation that carrying out an immunization protocol that induced an appropriate anti-antigen immune response in one animal would be reasonably expected to affect other members of the same species in a similar fashion. Thus, applicants respectfully submit that an immunization strategy that produced a decrease in PGC numbers and/or inhibited PGC development in one avian embryo would also be reasonably predicted to decrease PGC numbers and/or inhibit PGC development in another embryo within an egg produced by the same female.

As such, applicants respectfully submit that a trial in one or more members of a species that demonstrated that a "sufficiently high concentration" of antibodies was

present in an egg to decrease PGC numbers and/or inhibit PGC development would be reasonably predictive of a similar result using other members of the same species. Therefore, even if certain test avians needed to be sacrificed in order to determine appropriate immunization parameters to generate the desired response in a female avian, those same immunization parameters could be subsequently employed to perform the methods of claims 1 and 7 to prepare recipient avian embryos that could then be injected with donor PGCs.

Additionally, applicants respectfully submit that there is no basis for the Patent Office's apparent requirement that an individual embryo *per se* be tested *in ovo* to determine whether its PGC numbers were decreased or its PGC development was inhibited. Applicants respectfully submit that the embryos to which PGCs are transferred can be allowed to hatch and grow to sexual maturity, whereupon they can be bred to determine whether the transferred PGCs had colonized the germline. As set forth in the instant specification at page 1, line 31, through page 2, line 1, the efficiency of generating germline chimeras by repopulating the gonads with the desired donor PGCs can be enhanced by reducing the number of PGCs in the recipient organism. As such, applicants respectfully submit that one of ordinary skill in the art would also know how to test sexually mature chimeras for this enhanced germline chimerism relative to avians that had not been hatched from eggs from immunized mothers, thereby also providing evidence that the immunization scheme successfully decreased PGC numbers and/or inhibited PGC development in the avian as it developed in the egg.

Summarily, the Patent Office has constructed artificial requirements regarding the interpretation of the instant claims. The proper analysis of the claims under 35 U.S.C. § 112, second paragraph, only requires that the metes and bounds of the claims be understood by one of ordinary skill in the art after consideration of the specification. As set forth hereinabove, one of ordinary skill in the art would fully understand what is intended by the phrase sufficiently high concentration of antibodies specific for the antigen to decrease the PGC numbers and/or development in an avian embryo" as recited in claims 1 and 7, and thus the Patent Office has not presented a *prima facie* case of lack of compliance with the second paragraph of 35 U.S.C. § 112. Therefore,

applicants respectfully request that the instant rejection of claims 1-4 and 7-10 be withdrawn at this time.

IV.B. Response to the Second Rejection

The Patent Office has also rejected claims 1-4 and 7-10 under 35 U.S.C. § 112, second paragraph, on a second basis. According to the Patent Office, the metes and bounds of what applicants consider antibodies "specific for the antigen to decrease endogenous PGC numbers" (claims 1 and 7) are unclear. The Patent Office further asserts that the phrase "to decrease endogenous PGC numbers" is an intended use that may not occur, and thus it cannot be determined how specific the antibodies must be to decrease endogenous PGC numbers. From this, the Patent Office contends that those of skill would not be able to determine whether antibodies that recognized any DAZL antigen, for example, was encompassed by the claim of if the phrase was limited to antibodies that are specific to a particular DAZL antigen, *i.e.*, DAZL-C or DAZL-N.

Additionally, the Patent Office asserts the following:

> As written, the outcome is not directly linked to the antigen or the antibodies. The claims are not limited to administering antigens to an avian embryo, wherein the antigens are specific to avian PGCs, such that endogenous PGC numbers in the avian embryo decrease. The claims are not limited to administering an antigen to an avian embryo, such that antibodies that recognize the antigen are obtained, wherein the amount of antibodies obtained are sufficient to decrease endogenous PGC numbers in the avian embryo. As written, it is unclear how the specificity of the antibodies to the antigen relates to the outcome.

Final Official Action at pages 10-11. Applicants respectfully submit that these assertions demonstrate that the Patent Office has not considered the claims from the perspective of one of ordinary skill in the art in light of the specification.

To continue, applicants respectfully submit that the instantly claimed methods take advantage of the ability of the adult female avian that is immunized to produce anti-antigen antibodies, which are deposited in the eggs produced by the immunized females. These antibodies are then available for binding to the antigens present on the developing PGCs and/or their progenitors in accordance with the presently disclosed and claimed subject matter.

Secondly, applicants respectfully traverse the Patent Office's assertion that as written, the outcome of the methods of claims 1 and 7 is not directly linked to the antigen or the antibodies. Applicants respectfully submit that as set forth in the instant specification, the antibodies produced by the female bind to the antigens present in the developing embryo, and the outcome is that PGC numbers in the embryo are decreased and/or PGC development in the embryo is inhibited. Applicants respectfully submit that this would be clearly understood by one of ordinary skill in the art after review of the instant specification, and thus there is no need for the claims to explicitly recite this relationship.

Nonetheless, in an effort to facilitate prosecution, applicants have amended claims 1 and 7 to recite *inter alia* that an egg produced by the female bird comprises a sufficiently high concentration of antibodies specific for the antigen to bind to the antigen expressed by an avian embryo within the egg to thereby decrease endogenous PGC numbers (claim 1) or inhibit development of PGCs (claim 7) in the avian embryo. Support for the amendments can be found throughout the specification as filed, including particularly at page 11, line 27, through page 12, line 4; page 25, lines 8-11; page 29, lines 5-7; and page 30, line 21, through page 31, line 1. As such, no new matter has been added by the amendments to the claims.

Applicants respectfully submit that as a result of the amendments, the relationship between the antibodies produced, the antigens in the embryos, and the outcome of the interaction between the antibodies and the antigen is explicitly recited in the claims. As a consequence, applicants respectfully request that the instant rejection of claims 1-4 and 7-10 be withdrawn at this time.

Applicants further respectfully submit that claims 1-4 and 7-10 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

V. Applicants' Remarks Regarding the Elected Species

As a part of the Patent Office's discussion of the rejection under 35 U.S.C. § 112, first paragraph, the Patent Office asserts that upon overcoming the rejection above, the claims will have to be limited to using the elected species of DAZL antigen. The Patent Office offers no rationale for this contention.

Applicants respectfully traverse the Patent Office's apparent requirement that the claims be limited to the elected species of DAZL antigen. Particularly, applicants respectfully submit that the Restriction/Election Requirement dated May 16, 2007 indicated that upon the allowance of a generic claim, applicants will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of the allowable generic claim(s) as provided by 37 C.F.R. § 1.141.

To elaborate, applicants respectfully submit that 37 C.F.R. § 1.141(a) states:

> Two or more independent and distinct inventions may not be claimed in one national application, except that more than one species of an invention, not to exceed a reasonable number, may be specifically claimed in different claims in one national application, provided the application also includes an allowable claim generic to all the claimed species and all the claims to species in excess of one are written in dependent form (§ 1.75) or otherwise include all the limitations of the generic claim (emphasis added).

Applicants respectfully submit that the species recited in claims 4 and 8 of the instant application include a reasonable number and further that the claimed species are written in dependent form. Applicants respectfully submit that since the Restriction/Election Requirement also indicated that all the claims are generic, upon allowance of any of claims 1-4 and 7-10, applicants are entitled to consideration of the other species recited in the claims, including but not limited to those set forth in claims 4 and 8.

Accordingly, applicants respectfully request that the Patent Office withdraw its apparent requirement that the claims be limited to the elected species of DAZL antigen.

CONCLUSIONS

Should there be any minor issues outstanding in this matter, the Examiner is respectfully requested to telephone the undersigned attorney. Early passage of the subject application to issue is earnestly solicited.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any fees associated with the filing of this correspondence to Deposit Account Number **50-0426**.

Respectfully submitted,

JENKINS, WILSON, TAYLOR & HUNT, P.A.

Date: April 9, 2009

By: _____

Arles A. Taylor, Jr.
Registration No. 39,395
Customer No. 25297
(919) 493-8000

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